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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,489	02/26/2004	Samuel Zalipsky	ALZ5015 R1	7993

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EXAMINER	
SCHLIENTZ, LEAH H	
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1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,489	ZALIPSKY ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/26/04 ad 10/17/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 11/19/2007, in reply to the Office Action mailed 5/21/2007, is acknowledged and has been entered. Claims 1, 12 and 14 have been amended. Claim 11 has been cancelled. New claims 16 – 27 have been added. Claims 1 – 10 and 12 – 27 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, see page 7 of the Response, with respect to the rejection of claims 1 – 10 under 35 USC 102(b) as being anticipated by Zalipsky *et al.* (WO 01/05873) have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 7 – 10 of the Response, with respect to the rejection of claims 1 – 13 under 35 USC 103(a) as being unpatentable over Zalipsky *et al.* (WO 01/05873) in view of Watanabe *et al.* (US 5,786,387) have been fully considered and are persuasive. Therefore the rejection has been WITHDRAWN.

Applicant's arguments, see pages 7 – 10 of the Response, with respect to the rejection of claims 1 – 15 under 35 USC 103(a) as being unpatentable over Zalipsky *et*

al. (WO 01/05873) in view of Watanabe *et al.* (US 5,786,387), in further view of Abra *et al.* (US 5,945,122) have been fully considered and are persuasive. Therefore the rejection has been WITHDRAWN.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 – 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of reducing liposome-induced complement activation upon in vivo administration of liposomes containing an entrapped therapeutic agent, comprising providing liposomes of a vesicle-forming lipid and between 1 – 10 mole percent of a neutral lipopolymer having the formula shown in claim 16, wherein ... L is selected from the group consisting of (i), (ii), and (iii)... with the proviso that (i) when L is -X-(C=O)-, X is not NH; and (ii) when L is -X-(C=O)-Y, Y is not NH when X is O, and the remainder vesicle-forming lipids.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may

be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Note that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a prima facie case for lack of descriptive support. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993). See MPEP § 2163 - § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph.

In the instant case, the disclosure as originally filed does not provide support for the instantly claimed limitation wherein "(ii) when L is -X-(C=O)-Y, Y is not NH when X is O." See MPEP 2173.05(i). For example, there is no disclosure of a teaching that "L is -X-(C=O)-Y," thus such a component cannot be explicitly excluded. This is a new matter rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 – 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The claims are drawn to a method of reducing liposome-induced complement activation upon in vivo administration of liposomes containing an entrapped therapeutic agent, comprising providing liposomes of a vesicle-forming lipid and between 1 – 10 mole percent of a neutral lipopolymer having the formula shown in claim 16, wherein ... L is selected from the group consisting of (i), (ii), and (iii)... with the proviso that (i) when L is -X-(C=O)-, X is not NH; and (ii) when L is -X-(C=O)-Y, Y is not NH when X is O, and the remainder vesicle-forming lipids. The limitation wherein "L is -X-(C=O)-Y, Y is not NH when X is O" is indefinite because -X-(C=O)-Y is not one of the components which L is specifically defined to be in the claim (i.e. one of components (i) – (iii) in the claim).

Claims 6, 7 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recites the limitation "wherein said preparing" in line 1 of the respective claims. There is insufficient antecedent basis for this limitation in the claim because there is no "preparing" step in independent claims 1 and 16.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16 – 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Zalipsky *et al.* (WO 01/05873).

Zalipsky discloses liposomes containing 1 – 10 mole percent of PEG-substituted neutral lipopolymers having the structure shown in claim 1. The structures may include ether or ester-linked uncharged lipopolymers, see Figures 2 A and B; page 7, lines 6 – 13, for example. The liposomes can be used to encapsulate a drug (abstract, page 6, lines 17 – 20 and page 8, line 3). The liposomes are administered via injection (page 8). The circulation time of liposomes containing the PEG-substituted neutral lipopolymers is increased (claim 10). It is noted that the Zalipsky does not specifically recite that the neutral lipopolymer-containing liposomes reduce liposome-induced complement activation upon *in vivo* administration. However, because the same liposomes were administered as in the instantly claimed methods, such methods were inherently accomplished by Zalipsky upon administration of the liposomes to increase circulation time of the liposomes. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make a claim patentable. See *In re Best,* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) and MPEP 2112. Provided that the only step that is required for reduction of complement activation is providing the liposomes, as claimed, Zalipsky provided the same liposomes and thus meets the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

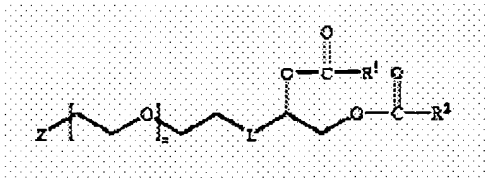
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 – 10, 12, 13 and 16 – 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky (WO 01/05873, whereby US 6,586,001 is relied upon as equivalent), in view of Watanabe *et al.* (US 5,786,387), in further view of Szebeni *et al.* (*J. Liposome Research*, 2002, 12, p. 165 – 172).

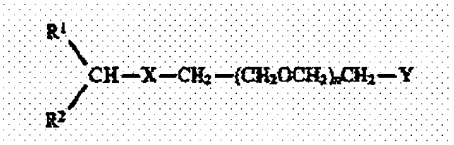
Zalipsky discloses liposomal compositions comprising 1 – 10 mole percent of a neutral lipopolymer having the formula as disclosed in claims 1 – 9 of US '001, and as shown below. See also Figures 1 and 2A - 2D, for example, including structures wherein L is an ether, ester, etc. linkage.



The liposomes can be used to encapsulate a drug (abstract, column 1, and column 4, lines 22—25), and are used in methods of increasing the circulation time of a liposome (claim 10).

Zalipsky does not specifically teach that the drug which may be encapsulated is a chemotherapeutic drug, and that the liposomes are used to decrease complement activation upon in vivo administration.

Watanabe teaches a lipid double chain derivative containing a polyoxyethylene which is used as a fine particle drug carrier such as a mixed micelle or lipid emulsion or a liposome (column 1, lines 10 – 15). The lipid double chain derivative compound containing a PEO moiety has the following structure:



While it is noted that Watanabe teaches a variety of compounds, the compounds of Watanabe are the same as those of Zalipsky, for example, when R^1 is R^3-CO_2-CH_2—, R^2 is R^3CO_2— and R^3 is alkyl. X may be -CO-NH-, -CO-O-, -NH-CO-CH^2-O-, -CH_2-O-CO-CH_2-O-, etc. for, example, and Y may be alkoxy or hydroxyl (column 2, lines 15+). The compounds can be incorporated into liposomes and may be used as drug carriers (column 7, lines 34+). Drugs which can be carried include anticancer drugs, preferably adriamycin (i.e. doxorubicin) or methotrexate (column 8, lines 1 – 6).

Watanabe does not specifically teach that the liposomes comprise from 1 – 10 mole percent of the PEG-substituted lipopolymer compounds, and does not teach that the compounds are used to decrease complement activation upon in vivo administration.

Szebeni discloses that negatively charged liposome vesicles comprising Doxil, HPL, pegylated phosphatidylethanolamine (PEG-PE) and phosphatidylglycerol (PG)-containing liposomes were potent complement activators in human serum in vivo, whereas small neutral liposomes caused no complement activation. Data suggests that liposome-induced hypersensitivity reaction (HSR) in susceptible individuals may be due to complement activation, which in turn is due to the presence of negatively charged PEG-PE in these vesicles (abstract). See also page 167, wherein it was determined that "negative charge on liposome surface plays a key, if not sole role in complement activation," and page 169, wherein Szebeni discloses that "Doxil, Doxil placebo and negatively charged liposomes caused severe to lethal cardiopulmonary distress in pigs, while neutral vesicles were without effect."

It would have been obvious to one of ordinary skill in the art to include anticancer drugs, such as adriamycin, methotrexate, etc. in the liposomes taught by Zalipsky who teaches that drugs are encapsulated in the liposomes. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Watanabe teaches that such anticancer drugs are capable of being encapsulated by liposomes comprising the same lipopolymers, and may be useful for cancer therapy. Both Zalipsky and Watanabe are drawn to PEGylated lipid derivatives and their

incorporation into liposomes for the purposes of drug delivery and long circulation times in the blood.

It would have been further obvious to utilize the liposomes comprising the neutral lipopolymers in methods of reduction of complement activation as compared to liposomes comprising negatively charged pegylated phospholipids. Zalipsky teaches that "the most commonly used PEG-substituted phospholipids are based on PE, which is negatively charged at the polar head group, and that negative surface charge in a liposome can be disadvantageous in some aspects, e.g. in interactions with cells and the delivery of cationic drugs, where leakage may occur" (column 1, lines 25 – 67). In addition to the advantages of incorporating the neutral lipids into liposomes, such as reduced leakage of encapsulated cationic drug and greater flexibility of monitoring interactions of the liposomal surface with target cells as compared to liposomes containing negatively charged PEG-PE (Zalipsky, column 1 and column 4, lines 22 - 27), it would have been obvious to utilize the liposomes comprising the neutral lipopolymers of Zalipsky and/or Watanabe to reduce complement activation, and thus liposome-induced hypersensivity reactions, upon in vivo administration because Szebeni specifically teaches that negative charge on liposome surface plays a key, if not sole role in complement activation, and that neutral vesicles caused no complement activation (abstract and pages 167 and 169). Thus one would have had a reasonable expectation of success that liposomes comprising the neutral lipopolymers of Zalipsky and/or Watanabe would have reduced complement activation properties as compared to liposomes comprising negatively charged lipids.

Claims 14, 15, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky *et al.* (WO 01/05873), in view of Watanabe *et al.* (US 5,786,387), in further view of Szebeni as applied to claims 1 – 10, 12, 13 and 16 – 25 above, in further view of Abra *et al.* (US 5,945,122).

The rejection over the teachings of Zalipsky, Watanabe and Szebeni is applied as above. Zalipsky, Watanabe and Szebeni do not specifically recite cisplatin as the anticancer drug which is encapsulated.

Abra teaches a liposome composition containing an entrapped cisplatin compound (abstract). The liposomes are composed of a vesicle-forming lipid and between about 1-20 mole percent of a vesicle-forming lipid derivatized with a hydrophilic polymer (i.e. PEG) (column 2, lines 10 – 38). The cisplatin is entrapped with substantially greater retention in the liposomes when compared to liposomes lacking the polymer coating (abstract).

It would have been further obvious to include cisplatin as the anticancer drug which is encapsulated because Abra teaches that cisplatin is an anticancer drug which is difficult to encapsulate in liposomes because drug retention can be a problem, but that encapsulation can be improved upon the incorporation of PEG into the liposome (abstract and column 1, line 63 – column 2, line 10). One would have been motivated to do, and would have had a reasonable expectation of success in doing so, because Zalipsky teaches that his liposomes provide advantages such as reduced leakage of an encapsulated cationic drug (page 6, line 18).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER